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APPELLANTS' REPLY BRIEF UNDER 37 C.F.R. §1.193(b)(1) Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket Confirmation No.	STAN-084 3881
	First Named Inventor	A. Hsueh
	Application Number	09/647,067
	Filing Date	September 25, 2000
	Group Art Unit	1647
	Examiner Name	B.E. Bunner
	Title	*Novel mammalian G-protein coupled receptors having extracellular leucine rich repeat regions*

Sir:

This Reply Brief is submitted in response to the Examiner's Answer dated September 20, 2004, for which a two-month period for response was given, making this Reply Brief due on or before November 20, 2004. Accordingly, this Reply Brief is timely filed.

In view of the remarks set forth below, reconsideration and allowance are respectfully requested.

I. REMARKS

Oral Hearing

Under 37 C.F.R.§1.194(b), if Appellant desires an Oral Hearing, appellant must file, in a separate paper, a written request for such hearing accompanied by the fee set forth in 37 C.F.R.§1.17(d) within two months from the date of the Examiner's Answer.

Appellants provide herewith a Request for Oral Hearing.

Rejection of claims 1, 2, 4, 7-11, and 18-20 under 35 U.S.C.§101

Claims 1, 2, 4, 7-11, and 18-20 were rejected under 35 U.S.C.§101 as allegedly lacking utility. In support of this rejection, the Office argued that the rejected claims are not supported by either a specific and substantial asserted utility or a well established utility.

The April 23, 2003 final Office Action stated that novel biological molecules lack well established utility and must undergo extensive experimentation. The April 23, 2003 final Office Action stated that the asserted utilities are credible, but not specific or substantial.

These statements and arguments were reiterated in the Examiner's Answer.

The Examiner's Answer acknowledged that the instant specification discloses that LGR7 polypeptides share structural similarity with other, known G protein coupled receptors (GPCR), such as leutinizing hormone (LH) receptor, follicle stimulating hormone (FSH) receptor, and thyrotropin (TSH) receptor. The Examiner's Answer then asserted that Appellant's position that the disclosed LGR7 polypeptides have biological activities similar to known GPCR family members with large extracellular leucine-rich repeat regions ("ectodomains") cannot be accepted in view of the existence of other polypeptide families wherein individual members have distinct, and even opposite, biological activities. However, Appellants have not asserted that LGR7 has an identical activity to the few other known ectodomain-containing GPCR. Instead, as noted previously, the specification states that LGR7 polypeptide bind a hormone ligand.

As noted previously, LGR7 is similar to other, previously known GPCR in that it exhibits the characteristic seven transmembrane feature. However, LGR7 differs from the vast majority of known GPCR in that it further exhibits a large extra-cellular leucine-rich repeat region ("ectodomain"). Specification, page 3, lines 26-29. The ectodomain found in LGR7 is structurally similar to that found in the previously described LH, FSH, and TSH receptors. Specification, page 3, line 29 to page 4, line 1; and page 1, lines 13-19. The large extracellular, leucine-rich domain of the LH, FSH, and TSH receptors, which domain is also referred to as an ectodomain, is believed to bind the corresponding hormone ligand. Specification, page 1, lines 13-19. Based on the disclosed close structural similarity of LGR7 to LH, FSH, and TSH receptors, LGR7 is disclosed to bind a hormone. Peptide hormone receptors such as LH, FSH, and TSH receptors have a well-established use in the art. Based on the disclosed close structural similarity of LGR7 to known peptide hormone-binding GPCR, LGR7 also has a well-established utility.

The Examiner's Answer stated that the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. However, Appellants did in fact correctly assert that LGR7, like LH, FSH, and TSH receptors, binds a hormone.

The Examiner's Answer acknowledged that the specification teaches that the LGR7 polynucleotide is useful for producing LGR7 polypeptides, which in turn are useful for drug screening for agonists and antagonists, and for neutralizing the action of an endogenous ligand. The Examiner's Answer stated that the asserted utilities are credible, but not specific or substantial, as the asserted utilities "can be performed with any polypeptide." Examiner's Answer, page 7. However, screening for agonists and antagonists of a hormone receptor cannot be carried out with "any polypeptide." Furthermore, neutralizing the action of an endogenous hormone ligand cannot be carried out with "any polypeptide." The polypeptide must be one that binds a hormone ligand, and that is what LGR7 does.

The Examiner's Answer stated that the specification does not disclose any methods or working examples that demonstrate that the instant polypeptides exhibit any activity. Appellants note that such is not a requirement under 35 U.S.C.§101. The Examiner's Answer stated that the skilled artisan would not be able to categorize the instant polypeptides as a GPCR, or a GPCR with an extracellular leucine-rich repeat region. However, that is exactly what Appellants did. As discussed previously, and as discussed in the specification, LGR7 was identified as a hormone-binding GPCR belonging to a small

subset of GPCR that share the feature of a large ectodomain.

The Examiner's Answer stated that the instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Supreme Court, 1966). The Examiner's Answer stated that in *Brenner*, a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent. The instant case differs from *Brenner*. In *Brenner*, the claims were not directed to a compound; rather, to a process for producing a compound, which compound was apparently known. In *Brenner*, there was apparently no disclosure of any utility for the compound synthesized by the claimed process. In the instant case, Appellants asserted that LGR7 binds a hormone ligand; and Appellants subsequently demonstrated experimentally that LGR7 does indeed bind a hormone. See, Hsu et al. ((2000) *Molec. Endocrinol.* 14:1257-1271; "Hsu (2000)"; a copy of which was provided as Exhibit 2 in the amendment, filed on February 3, 2003 and responsive to the November 6, 2002 Office Action. As discussed in the Appeal Brief, Appellants provided experimental data demonstrating that LGR7 binds a hormone, i.e., relaxin; Appellants generated a soluble LGR7 ectodomain, as discussed in the instant application; and demonstrated that the soluble extracellular domain of LGR7 functions as an antagonist to LGR7, neutralizing the action of the ligand relaxin, as discussed in the instant application.

Rejection of claims 1, 2, 4, 7-11, and 19-20 under 35 U.S.C.§112, first paragraph

Claims 1, 2, 4, 7-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement in view of the rejection of these claims under 35 U.S.C.§101. Claims 1, 7-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. Claims 1, 7-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking written description.

Claims 1, 2, 4, 7-11, and 18-20; enablement

Claims 1, 2, 4, 7-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. In support of this rejection, the Office argued that the rejected claims are not supported by either a specific and substantial asserted utility or a well established utility; and that one skilled in the art would not know how to use the invention. Appellants' position on this issue has been made of record in the Appeal Brief. It is Appellants' position that, in view of Appellants' position that the instant claims meet the requirements of 35 U.S.C.§101, those skilled in the art would also know how

to use the claimed invention.

Claims 1, 7-11, and 18-20; enablement

Claims 1, 7-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement. The Examiner's Answer stated that the skilled artisan would not know how to make and use the LGR7 nucleic acid fragments and variants comprising an isolated nucleic acid encoding a mammalian LGR7 protein, wherein the LGR7 protein comprises an amino acid sequence having at least 80% or at least 90% amino acid sequence identity to the sequence set forth in SEQ ID NO:8. The Examiner's Answer stated that the specification also does not provide evidence to demonstrate that a skilled artisan would know how to make and use fragments and variants of LGR7 that have at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO:8.

The Examiner's Answer acknowledged that the enablement issue does not apply to claims 2 and 4, which recite, respectively, that the LGR7 protein has the amino acid sequence of SEQ ID NO:8, and that the nucleotide sequence of the nucleic acid has the sequence set forth in SEQ ID NO:7, or the complementary sequence thereof.

Appellants' position with respect to the enablement rejection has been made of record, during prosecution, and in Appellant's Appeal Brief. The Examiner's Answer stated that the specification does not teach LGR7 nucleic acid variant or polypeptide variants. However, as discussed during prosecution and in the Appeal Brief, the specification does teach LGR7 nucleic acid and polypeptide variants. The specification provides the nucleotide and amino acid sequences of at least two LGR7 polypeptides. The Examiner's Answer stated that the specification does not teach any functional or structural characteristics of the variants or fragments of the nucleic acid of SEQ ID NO:7 or the polypeptide of SEQ ID NO:8. However, as discussed in during prosecution and in the Appeal Brief, the specification teaches fragments of LGR7 and discusses the functional characteristics of such fragments. The specification discusses the extracellular domain of LGR7, and states that this ectodomain is useful, e.g., in the neutralization of the action of endogenous ligands.

The Examiner's Answer discusses the alleged unpredictability of predicting protein structure from sequence data; and states that undue experimentation would be required of the skilled artisan to make and/or use the claimed invention. However, as discussed during prosecution and in the Appeal

Brief, as of the March 26, 1998 priority date, those of ordinary skill in the art, given the guidance in the instant specification, coupled with the extensive knowledge and high skill level in the art, could readily make LGR7 fragments and variants, and determine their activity, e.g., hormone binding activity.

As noted previously, practitioners in the molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[1]

The skill level in the art was high as of the March 26, 1998 priority date. The relevant ordinarily skilled artisan considered it routine to make nucleic acid fragments and variants, and to test polypeptide fragments and variants encoded by such nucleic acid fragments and variants.

As pointed out in the Appeal Brief, Hsu (2000), carrying out nothing more than routine experimentation, identified amino acid residues essential for function of the LGR7. Thus, given the information provided in the instant specification, combined with the skill and knowledge in the art, those skilled in the art could readily and without undue experimentation identify and mutate amino acid residues important for the function of an LGR7 polypeptide as a GPCR.

Furthermore, as pointed out in the Appeal Brief, Hsu (2002), carrying out nothing more than routine experimentation, generated a soluble LGR7 ectodomain, and demonstrated that a soluble extracellular domain of LGR7 functions as an antagonist to LGR7, neutralizing the action of the ligand relaxin. Thus, those skilled in the art, given the guidance in the specification, would know which fragments of LGR7 would be expected to function as discussed in the specification.

Claims 1, 7-11, and 18-20; written description

Claims 1, 7-11, and 18-20 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking written description. The Examiner's Answer stated that the rejection of claims 2 and 4 under 35

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1 *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

U.S.C.§112, first paragraph, is withdrawn.

The Examiner's Answer stated that the "description of two LGR7 polynucleotides and polypeptides (SEQ ID NOs:6,8) in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, and fragments of the nucleic acid sequence that encodes an amino acid sequence having at least 80% amino acid sequence identity of SEQ ID NO:8 or all mutants, derivatives, and fragments of amino acid sequences of SEQ ID NO:8." Examiner's Answer, page 13. Appellants' position on this issue has already been made of record, during prosecution and in Appellants' Appeal Brief.

The Examiner has not reviewed the instant claims for compliance with the written description requirement in a manner consistent with the U.S. Patent Office's Written Description Guidelines.

According to U.S. Patent Office guidelines, a review of whether a patent application meets the written description requirement of 35 U.S.C.§112, first paragraph, is conducted from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art.

According to U.S. Patent Office guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species; and that a "representative number of species" means that the species which are adequately described are representative of the entire genus. The Written Description Guidelines state that there may be situations in which one species adequately supports a genus; and that what constitutes a "representative number" is an inverse function of the skill and knowledge in the art.[2]

The Examiner has merely stated that the description of two LGR7 polynucleotides and polypeptides in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides. The Examiner has not presented evidence or reasons why a person skilled in the art

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2 Written Description Guidelines, page 1106.

would not recognize that the written description of the invention provides support for the claims.

The Examiner has not conducted a review of the claims *from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art.* Had the claims been examined from the standpoint of one of skill in the art as of the March 26, 1998 priority date of the instant application, the claims could not have reasonably been rejected as lacking adequate written description, because those skilled in the art would have concluded that Appellants had possession of the claimed invention.

Even though the Examiner's Answer acknowledged that Appellants disclosed at least two different LGR7 nucleic acids and polypeptides, the Examiner's Answer completely ignored the skill level as of the March 26, 1998 priority date.

As previously discussed, as shown in Figure 5 of the instant application, the polynucleotides identified as SEQ ID NO:05 and SEQ ID NO:07 encode the polypeptides identified as SEQ ID NO:06 and 08, respectively. Both SEQ ID NO:06 and 08 are LGR7 polypeptides. The specification states that the LGR7 polypeptides are encoded by splice variants. Specification, page 25, lines 15-25. Furthermore, as discussed above, the specification provides a description of various fragments of LGR7 polypeptides, e.g., a soluble ectodomain of LGR7, and uses thereof. Still further, the skill level in the art as of March 26, 1998 was extremely high. Those skilled in the art would have recognized that Appellants, as of the March 26, 1998 priority date, had possession of the claimed invention. Thus, the specification provides adequate written description for the claimed nucleic acids and polypeptides.

II. CONCLUSION

Appellants present evidence that the subject claims meet the requirements of 35 U.S.C.§101, as well as the requirements of 35 U.S.C.§112, first paragraph. Additional arguments have already been presented, both in responses to Office Actions during the course of prosecution, as well as in Appellants' Brief. In view of the remarks set forth above, and those already of record, Appellants respectfully request that the above-discussed rejections be withdrawn, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-084.

Respectfully submitted,
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Date: Nov. 19, 2004

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